REMARKS

Claims 2-38 are pending. Applicants have amended claim 2 to recite that step c) of producing amplified RNA from the double stranded cDNA is done "in a reaction which is completed in 180 minutes or less" in this response. This language is supported in the application as filed, e.g., at page 5, lines 5-6 and 24-25. Thus, the amendment adds no new matter.

Applicants acknowledge the Examiner's withdrawal of earlier rejections and the consideration of the IDS filed on July 30, 2009.

Non-Statutory Double Patenting

The Office alleges that claims 2 to 38 are either anticipated by or obvious in view of claims 1 to 32 of U.S. Patent No. 6,794,141 ("the '141 patent"). Applicants respectfully traverse this rejection, because the present claims are neither anticipated by nor obvious in view of any of the **claims** of the '141 patent.

First the Office alleges that claims 2 and 21 of the present application "are anticipated by the claims 1, 6, 10, 17, and 23 of the patent '141" (Office Action at page 3), because "claims 1, 6, 10, 17, and 23 of the patent '141 fall entirely within the scope of claims 2 and 21" of the present application (*id.*).

Second, the Office alleges that "[t]he only obvious variation is that the instant claims recite incubation periods of first and second strand synthesis, *which is fully supported by the disclosure of the patent* '141 (see at least col. 15, line 56-67, col. 16, 1-12), which is considered as an obvious variation. Thus the instant claims encompass the claims in the patent ('141) and are related as genus and species, and are coextensive in scope" (Office Action at pages 3-4, emphasis added). Thus, the Office appears to be saying that the present claims cover a genus, and the '141 patent claims recite species.

Applicants respectfully submit that the present claims are neither anticipated by nor obvious in view of the claims of the '141 patent. First, the recited steps in the present claims and in the claims of the '141 patent are clearly different, as is the scope of these claims. They are not coextensive in scope as the Office alleges. Second, it is inappropriate and contrary to legal

precedent for the Office to cite language in the specification of the '141 patent describing specific incubation periods as the basis for the present obviousness-type double patenting rejection.

A non-statutory, obviousness-type double patenting rejection is appropriate only where an application claim is not patentably distinct from the reference claim of a patent because the application claim is either anticipated by, or would have been obvious over, the reference *claim(s)*. MPEP 804(II)(B)(1) (emphasis added).

Analysis for obviousness-type double patenting involves two steps. First, the claims in the earlier patent or patent application and the later application are construed and the differences between them are determined; second, a determination is made as to whether the differences in the subject matter between the earlier and later *claims* render both claims patentably distinct. *Eli Lilly & Co. v. Barr Labs., Inc.,* 251 F.3d 955, 968 (Fed. Cir. 2001)(emphasis added). Stated another way, the *claim* in an earlier patent or patent application is compared to the *claim* in a later patent or patent application. *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed.Cir.2003)(emphasis added).

"Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the *claims* in the multiple patents or patent applications involved in the analysis." MPEP 804 (emphasis added). It is important to remember that "[w]hen considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, **the disclosure of the patent may not be used as prior art**." MPEP 804(II)(B)(1) citing *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279 (Fed. Cir. 1992))(emphasis added). An analysis for obviousness-type double patenting that is not based on anticipation is therefore very similar to an analysis of obviousness under 35 U.S.C. § 103(a), **except that the specification of the patent underlying the double patenting rejection is not considered prior art**. *In re Longi*, 759 F.2d 887, 892 n. 4, (Fed. Cir. 1985).

Here, the '141 patent clearly does not **claim** any time limits for the completion of reactions, and most certainly does not claim a 45 minutes time limit (as recited in steps a and b of

independent claim 2) or a 180 minute time limit (as recited in step c of claim 2). It is simply not relevant to a double patenting analysis that the *specification* of the '141 patent may recite certain time limits. Thus, applicants respectfully request that the Examiner reconsider and withdraw the double-patenting rejection.

35 U.S.C. § 103

Claims 2-38 have been rejected as being allegedly unpatentable over Ziman et al. (U.S. 2004/0081978A1; "Ziman") in view of Godfrey et al. (U.S. Patent No. 7,101,663; "Godfrey"). Applicants traverse this rejection for the following reasons.

According to the Office Action at page 3,

> Ziman et al. teach a method of claim 2, 9-10, 20, 28-29, 38, for producing amplified RNA (aRNA) comprising
> (a) reverse transcribing an RNA template using a promoter-primer complex and an RNA dependent DNA polymerase (reverse transcriptase enzyme) to produce a first strand cDNA (see page 5, paragraph 0041-0042, 0035-0036, page 6, paragraph 0048)
> (b) treating the reverse transcription product with RNAse H enzymatic activity (see page 5, paragraph 0040, page 6, paragraph 0048);
> (c) producing a second strand cDNA complementary to said first strand cDNA using a DNA dependent polymerase, in the presence of random primers to prime the synthesis of said second strand cDNA (see page 5, paragraph 0043-0045;
> (d) producing amplified RNA from the eluted double stranded cDNA by in vitro transcription using a DNA dependent RNA polymerase which initiates transcription from the promoter-primer complex (see page 6, paragraph 0050-0056);
> wherein the product produced after c), after d) or both is purified by contacting said product with a solid phase (Qiagen column) which binds nucleic acids followed by eluting bound nucleic acids from the solid phase dissolved in less than 50 ul (see page 9, paragraph 0084).

First, applicants note that the feature cited above, "(b) treating the reverse transcription product with RNAse H enzymatic activity" is no longer recited in applicants' claim 2 or any

other claim. Other recitations in the language of the Office Action quoted above also fail to track the present language of independent claim 2.

Second, the Office concedes (at page 6 of the Action) that, "Ziman et al. did not specifically teach completion of each of the first and second cDNA synthesis steps in less than 45 minutes," but alleges that, "Godfrey et al. teach rapid RT-PCR method which is performed in less than 10 minutes (see col. 2, line 62-67, col. 3, line 1-3)" (id.). The Office then concludes (at page 6):

> [i]t would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of producing aRNA as taught by Ziman et al. with a step of completing the method steps in less than 45 minutes as taught by Godfrey et al. to achieve [the] expected advantage of developing a sensitive and enhanced method of producing aRNA. An ordinary practitioner would have been motivated to combine the teaching of Ziman et al. with the step of completing the reaction in less time as taught by Godfrey et al. because one skilled in the art would have a reasonable expectation of success that the combination would result in a rapid, automated method for RT-PCR (see col. 2, line 62-67, col. 3, line 1-3) and such modification of the method would be considered as obvious over cited prior art" (Office Action at pages 6-7).

The Office also notes that "[r]outine optimization is not considered inventive and no evidence has been presented that the selection of hybridization conditions performed was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art" (Action at page 7).

Applicants respectfully disagree for at least three reasons. First, it is improper to combine the "fast reaction" RT-PCR methods of Godfrey with the methods of Ziman, because these methods are quite different and serve different purposes. Godfrey's method requires specific primer concentrations and relies heavily on specific primer sets, and thus would not have been expected to work with the random primers used in Ziman's method and vice versa. Second, as admitted by the Office, Ziman fails to recite the completion of either steps a) or b) in claim 2 in 45 minutes or less, much less completing both steps together in less than 90 minutes. Third, applicants have amended claim step c) to require completion of this reaction step in 180 minutes

or less. Thus, the combined maximum time for steps a), b), and c) is only 270 minutes or less. This total time is so much faster than the total time of over 18 hours for Ziman's method that the difference cannot justifiably be referred to as merely "routine optimization."

Applicants will now explain these three reasons in greater detail.

First, Godfrey does not remedy the deficits of Ziman, and the short processing times of Godfrey cannot simply be applied to Ziman's methods as the Office suggests. In particular, Ziman uses random primers in the amplification step for the purpose of amplifying an entire mRNA message. On the other hand, Godfrey uses "substantially increased primer concentrations" (at column 5, lines 66-67) of specific primers to be able to achieve his rapid PCR methods. Godfrey clearly states that "the specificity of any given PCR reaction relies heavily, but not exclusively, on the identity of the primer sets" (column 6, lines 7-8). Godfrey also describes the use of high concentrations of "PCR primer sets specific to the cDNA" and "reverse-transcriptase-optimized and PCR-optimized primers" to achieve good results (at column 6, lines 58-59 and 65). Similarly, in the Examples, Godfrey notes the use of specific primers, such as CEA primers used in Example 4 that were designed to span a junction between specific exons of CEA mRNA. Applicants have carefully reviewed Godfrey, and the only reference to the use of a random primer is in Example 1, in a test of the effect of a wax layer on the ability of the system to detect fluorescence (see column 16, lines 46-55). This description is totally irrelevant to an analysis of obviousness of the present claims.

Substitution of random primers into Godfrey's method would render it inoperative; it would no longer detect or quantify specific messages. Likewise, substitution of specific primers into Ziman's method would render it inoperative; it would amplify only selected messages, not the entire message. So the Office's proposed combination of the methods of Ziman and Godfrey has no factual support and is therefore improper.

Second, while applicants' claim 2 recites that the first two steps to produce double-stranded cDNA must be completed within 90 minutes, Ziman recites completing his cDNA synthesis reaction in a time of at least 120 minutes (see paragraphs 0216-0219, at page 17). This is a clear difference.

Third, Ziman discloses that his methods require RNA transcription incubation times of 16 hours (see, e.g., paragraphs 0057 and 0222). In addition, as noted above Ziman discloses that prior steps before the transcription step take well over two hours. Additional incubation steps amount to another 35 minutes (see paragraphs 0213-0222, which outline the procedures in Example 1). Thus, the main steps in the Ziman method take 18 hours (1080 minutes), and the entire process takes at least 18 hours and 35 minutes. Comparing just the main steps, Ziman takes 1080 minutes, and applicants' claim 2 recites that steps a), b), and c) must be completed in less than 270 minutes (and dependent claim 20 recites a total of less than 230 minutes). Thus, the Ziman method takes at least four times longer.

Based on these facts, one of skill in the field would not have thought that one could use the random primer method of Ziman (which requires at least 18 hours of processing time) with the rapid process steps of Godfrey as the Office alleges, because Godfrey requires specific primers and primer concentrations to achieve his rapid PCR reaction times, and thus in effect teaches away from the use random primers for rapid RT-PCR methods. Given these clear differences between Ziman's and Godfrey's methods, applicants submit that the Office has failed to establish a *prima facie* case of obviousness of claim 2, as none of the references, or any combination thereof, would provide the claimed invention. As a result, claim 2 is clearly patentable.

In addition, the presently claimed methods are not merely routine optimization as the Office alleges, because no one skilled in this field reading the Ziman application would have considered reducing the over 18 hours of processing times recited in Ziman's methods down to only 270 minutes or less as presently claimed, while still obtaining useful amplification results as described in the present application. So-called "routine optimization" might hypothetically have lead one of skill to reduce the times somewhat, but not a 4-fold reduction in time. Given the use of random primers in the Ziman method, one of skill would have had no reason to believe that the incubation times could be reduced as much as presently recited in applicants' claim 2.

As explained in the present specification (page 8, lines 3-9):

> ... the reduction in reaction times by terminating the reaction and/or moving onto the next action reflects a truncation in the amount of time available for the

> production of various reaction products. Thus the use of "completed" in the above means that a reaction is terminated or that the next reaction begins. This reflects the surprising observation that such decreased time periods are sufficient to produce material sufficient to permit amplification without significant differences in the observed level of amplification (emphasis added).

Thus, applicants' claimed methods allow efficient amplification of RNA in far less time than what a skilled practitioner would have expected to be necessary to produce an adequate amount of amplified RNA.

Moreover, contrary to what is asserted in the Office Action, a skilled practitioner would have had no reasonable expectation of success in performing such a method based on a review of Ziman and Godfrey. As discussed above, applicants' method reflects the surprising result that significantly decreased reaction times compared to Ziman's reaction times are sufficient to allow amplification of RNA. Thus, a skilled practitioner would not have expected to amplify RNA by using the claimed methods with random primers and with a much shorter overall reaction time. The Office has not pointed to any evidence to suggest otherwise, nor is there anything in the Ziman or Godfrey references that would have led a skilled practitioner to believe that the claimed combination of the use of random primers with very rapid reaction times would work at all to amplify RNA.

As a result, applicants request that the Examiner reconsider and withdraw the rejection of claim 2 under Section 103. Applicants submit that claims 3 to 38 all ultimately depend from claim 2, and are thus patentable for at least the same reasons.

CONCLUSION

Applicants submit that the all of the claims are in condition for allowance and request entry of the proposed amendments and confirmation of allowance by the Examiner. It is believed that all of the pending issues have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify applicants' agreement. In addition, because the arguments made above may not be exhaustive, there may be additional reasons for patentability of any or all pending claims (or other claims) that have not been expressed.

Further, the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Applicants submit herewith a request for a Two Month Extension of Time. A fee of $490.00 for the Two Month Extension of Time to and including March 15, 2010 (March 13, 2010 being a Saturday) is being paid concurrently with the Electronic Filing System (EFS). Please apply all charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14255-0052US1.

Respectfully submitted,

Date: March 15, 2010

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